	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4474893	October 1984	Reading	
☐	4722899	February 1988	Hamaoka et al.	
☐	4752582	June 1988	Vanderlaan et al.	
☐	4868109	September 1989	Lansdorp	
☐	5087570	February 1992	Weissman et al.	
☐	5137809	August 1992	Loken et al.	
☐	5262319	November 1993	Iwata et al.	

OTHER PUBLICATIONS

Knapp, W. et al. eds, Oxford University Press. Oxford, pp.818, Civin, C. et al., Report on the CD34 cluster workshop. In: Leucocyte typing IV, White Cell Differentiation Antigens, (1989).

Ishizawa, L. et al., In: Hematopoietic Stem Cells: The Mulhouse Manual eds. Winder, E. et al., 171-182, (1994).

Shpall, E.J., et al., J. of Clinical Oncology, 12:28-36, 1994.

Winslow, J.M., et al., Bone Marrow Transplantation, 14:265-271, 1994.

Thomas, T.E., Cancer Research, Therapy and Control, 4(2): 119-128), 1994.

Linch, D.C. and Nathan, D.G., Nature 312 20/27: 775-777, 1984.

Sieff, C.A., et al., Science 230: 1171-1173, 1985.

Kannourakis, G. and Bol, S., Exp. Hematol, 15:1103-1108, 1987.

Carlo-Stella et al., Blood 84, 10 supple:104a, 1994.

Reading, C., et al., Blood 84, 10supple.:399a, 1994.

Hodgson, G.S. & Bradley, T.R., Nature, vol. 281, pp. 381-382; (Oct. 1979).

Visser et al., J. Exp. Med., vol. 59, pp. 1576-1590, 1984.

Spangrude et al., Science, vol. 241:58-62, 1988.

Szilvassy et al., Blood, 74:930-939, 1989.

Ploemacher, R.E. & Brons, R.H.C., Exp. Hematol., 17:263-266, 1989.

Udomsakdi et al., Exp. Hematol., 19:338, 1991.

Sutherland et al., Proc. Natl. Acad. Sci., 87:3584, 1990.

Craig et al., British Journal of Haematology, 88:24-30, 1994.

Lansdorp, P.AI. and Dragowska, W., J. Exp. Med. 175:1501-1509, 1992.

Sutherland, H.J., et al., Blood 74.1563-1570, 1989.

Van Vlasselaer, P., Density Adjusted Cell Sorting (DACS), A Novel Method to Remove Tumor Cells From Peripheral Blood and Bone Marrow StemCell Transplants. (1995) 3rd International Symposium on Recent Advances in Hematopoietic Stem Cell Transplantation-Clinical Progress, New Technologies and Gene Therapy, San Diego, CA.

Berenson et al., Journal of Immunological Methods 91:11-19, 1986.

Nordon et al., Cytometry 16:25-33, 1994.

Molday, R.S. and MacKenzie, D., J. Immunol. Methods 52:353, 1982.

Thomas et al., J. Hematother. 2:297, 1993.

Thomas, T.E. et al., J. Immunol Methods 154:245;252, 1992.

Lansdorp, P.M. and Thomas, T.E., Mol. Immunol. 27:659-666, 1990.

Thoma et al., Blood, vol. 83(8), 2103-2114, 1994.

van der Schoot et al., Blood, vol. 76(9), 1853-1859, 1990.

Smeland et al., Leukemia, vol. 6(8), 845-852, 1992.

Paul, W.E., Fundamental Immunology, Chapter 8, Raven Press NY, 1993.

Sevier et al., Clinical Chemistry, vol. 27, No. 11, 1797-1806, 1981.

Seaver et al., Genetic Engineering News, vol. 14, No. 14, pp. 10 and 21, 1994.

Gabbianelli et al., Science, vol. 249, 1561-1564, Sep. 1990.

Saeland et al., Exp. Haematol., vol. 20:24-33, 1992.

Verfaillie et al., J. Exp. Med., vol. 172:509-520, Aug. 1990.

Berenson et al., Blood, vol. 67, No. 2, 509-515, Feb. 1986.

Greenwalkt et al., Blood, vol. 80, No. 5, 1105-1115, Sep. 1992.

Penninger et al., Immunol. Review, No. 135, 183-214, 1993.

Fischer et al., J. Immunology, vol. 144, No. 2, 638-641, Jan. 1990.

Kuijpers et al., J. Immunology, vol. 151, No. 9, 4934-4940, Nov. 1993.

Kuijpers et al., J. Cell. Biol., vol. 118, No. 2, 457-466, Jul. 1992.

Hakomori, Ann. Rev. Immunol., vol. 2, 103-126, 1984.

Ross, A.A. et al, ISHAGE '98, Baltimore, J. Hematother 7:1993, No. 3 (P29).

Shammo, J.M. et al, ISHAGE '98, Baltimore, J. Hematother 7:1993, No. 3 (P128).

Ross, A.A. et al., ISHAGE '98, Baltimore, J. Hematother 7:1993, No. 3 (P131).

Bosnes, M. et al., ISHAGE '98, Baltimore, J. Hematother 7:1993, No. 3 (P138).
Randen, I. et al., ISHAGE '98, Baltimore, J. Hematother 7:1993, No. 3 (P139).
Naume, B. et al., ISHAGE '98, Baltimore, J. Hematother 7:1993, No. 3 (P140).
Kruger, W.H.et al., ISHAGE '98, Baltimore, J. Hematother 7:1993, No. 3 (P137).
Moss et al., Blood, vol. 83, No. 10, 3085-3089, 1994.
Moss, T.J. and Ross, A.A., Journal of Hematotherapy, 1:225-232, 1992.
Brockstein, B.E. et al., Journal of Hematotherapy, 5:617-624, 1996.
Sharp, J.G. et al., Journal of Hematotherapy, 4:141-148, 1995.
Sharp, J.G., Journal of Hematotherapy, 5:519-524, 1996.
Chan, W.C. et al., Journal of Hematotherapy, 3:175-184, 1994.
Passos-Coelho, J.L. et al., Blood, vol. 85, No. 4, 1138-1143, 1995.
Racila, E. et al., Proc. Natl. Acad. Sci. USA, vol. 95, 4589-4594, Apr. 1998.
Moss, T.J. et al., Journal of Hematotherapy, 3:163-164, 1994.
Naume, B. et al. Jounral of Hematotherapy 6:103-114, 1997.
Rye, P.D., et al., American Journal of Pathology, vol. 150, No. 1, 99-106, Jan. 1997.
Denis, M.G. et al., Int. J. Cancer (Pred. Oncol.): 74, 540-544, 1997.
Eaton et al., Short Technical Reports, vol. 22, No. 1, Circle Reader Service No. 191-194, 1997.
Moss, T.J. and Kahn, D.J., Bone Marrow Transplantation, vol. 18, Suppl. 1, S17, 1996.
Moss, T.J., et al. Journal of Hematotherapy, 1:65-73, 1992.
Moss, T.J. et al. ISHAGE '98 Baltimore, J. Hematotherapy 7, No. 3:1998, No. 3 (P133), p. 299.
Clarke, C. et al., Epith Cell Biol 3:38-46, 1994.
Hardingham, J.E. et al. Mol. Med. Nov. 1995; 1(7):789-94, Abstract.
Tedder, T.F. and P.J. Jansen, Current Protocols in Immunology, 7.32.1-7.32.16, 1997.
Schuler, G. et al., Dendritic Cells: Biology and Clinical Applications, Academic Press, Chapter 27. pp. 515-533 (1999).
Metcalfe, D.D., Current Protocols in Immunology, Unit 7.24, pp. 7.24.1 to 7.24.4, 1991.

Swiggard, W.J. et al. Current Protocols in Immunology, Unit 3.7, pp. 3.7.1 to 3.7.11, 1992.

ART-UNIT: 162
PRIMARY-EXAMINER: Burke; Julie
ATTY-AGENT-FIRM: Bereskin & Parr

ABSTRACT:

The present invention relates to antibody composition that are useful in

preparing enriched cell preparations such as human hematopoietic progenitor cells and stem cells and non-hematopoietic tumor cells. The invention also relates to kits for carrying out the processes and to the cell preparations prepared by the processes.

11 Claims, 9 Drawing figures

Detailed Description Paragraph Center (18):
Enrichment of Breast Carcinoma Cells in Peripheral Blood

Detailed Description Paragraph Table (5):

TABLE 4
Antibodies Recognizing Non-Hematopoietic Antigens Expressed on Epithelial Tumor Cells.
Disease Antibody Antigen Supplier/Developer

Breast and
Lung 5E11 unknown, breast carcinoma STI Carcinoma 6E7 unknown, breast carcinoma STI
H23A unknown, breast carcinoma ATCC RAR9941 epithelial glycoprotein Baxter, Germany
RAR9948 epithelial glycoprotein Baxter, Germany RAR9938 crb2 Baxter, Germany C13B5 crb2
Immunotech, Marseille, France BRST 1 BCA 225 ID Labs BRST 3 TAG-72 ID Labs CA15.3
MAM-6, mucin ID Labs CA27.29 MAM-6, mucin Cedarlane BcrEp4 HEA DAKO Neuroblastoma UJ13A
unknown Hurko and Walsh (1983) Neurology 33:734 UJ181.4 unknown Hurko and Walsh (1983)
Neurology 33:734 UJ223.8 unknown Hurko and Walsh (1983) Neurology 33:734 UJ127.11
unknown Hurko and Walsh (1983) Neurology 33:734 5.1.H11 unknown Hurko and Walsh (1983)
Neurology 33:734 390,459 unknown R. C. Seeger, L.A. Children's Hospital, Calif. BA-1.2
unknown R. C. Seeger, L.A. Children's Hospital, Calif. HSAN 1.2 unknown Reynolds and
Smith (1982) Hybridomas in Cancer p235

Detailed Description Paragraph Table (8):

TABLE 7
Purging Breast Carcinoma Cells (BT20 or T47D cells). Anti-Breast Carcinoma Log Tumor
Cell Cell Type Lineage Depletion Antibodies Depletion

Previously
Frozen Bone Purge Only 5E11 1.8 Marrow 5E11, H23A 3.7, 3.7 5E11, 6E7 3.0 Previously
Frozen Bone Lineage Depletion and Purge 5E11 >5.8, 3.9, 4.7 Marrow RAR >5.8, 4.3, 4.7
BRST1 4.9 5E11, H23A >5.2, 4.4 5E11, RAR, BRST1 >5.8 Peripheral Blood Purge only 5E11
1.9, 1.9 Leukapheresis H23A 1.7 5E11, H23A 2.3 Peripheral Blood Lineage Depletion and
Purge 5E11, H23A 5.6 Leukapheresis Fresh Bone Marrow Lineage Depletion and Purge 5E11,
H23A 4.6, 4.4

Detailed Description Paragraph Table (10):

TABLE 9
Enrichment of CAMA Breast Carcinoma Tumor Cells From Bone Marrow # CAMA in % CAMA in %
CAMA in % Recovery Log Enrich. Exp # Sample Start Start Flow CAMA CAMA

1 BM
1.1/10.sup.2 1.06 91.07 72.41 1.9 2 BM 2.2/10.sup.2 2.18 96.40 44.12 1.6 2.1/10.sup.3
0.21 82.16 75.00 2.6 2.1/10.sup.4 0.02 32.01 60.00 3.2 3 BM 2.6/10.sup.3 0.26 62.54 *
2.4 2.6/10.sup.4 0.026 11.21 * 2.6 2.6/10.sup.5 0.0026 2.01 * 2.9 2.6/10.sup.6 0.00026
0.13 * 2.7
*Cell numbers were too low to count accurately.

Detailed Description Paragraph Table (11):

TABLE 10   Purity, Recovery, and Enrichment of
CAMA Breast Carcinoma Tumor Cells Seeded into Previously Frozen Peripheral Blood
Mononuclear Cells Start Enriched Fraction % Purity % Purity % Recovery Log Enrichment
0.3 95.5 9.0 2.5 0.03 65.3 13.3 3.4 0.003 17.1
12.1 3.8 0.3 96.7 14.3 2.5 0.03 52.4 13.1 3.3 0.003 82.7 14.8 4.5 0.3 92.7 25.8 2.5
0.03 61.4 17.0 3.3 0.003 16.8 7.0 3.7 0.3 91.2 14.5 2.5 0.03 61.3 17.9 3.3 0.003 18.0
8.0 3.8 0.02 24.5 47.2 3.1 0.02 9.3 42.9 2.7 0.1 97.7 85.8 2.9 0.01 81.0 86.1 3.9 0.001
21.4 62.1 4.3 0.004 6.6 4.4 3.2 0.03 42.8 12.5 3.2 0.02 35.7 12.8 3.3 0.01 40.4 62.3
3.5 0.01 36.3 54.2 3.4 0.01 33.7 53.0 3.4 0.02 43.3 25.2 3.4 0.02 52.9 38.1 3.5 0.02
26.9 113.0 3.2 0.02 34.7 71.9 3.3

Detailed Description Paragraph Table (12):

TABLE 11   Purity and Enrichment of CAMA Breast
Carcinoma Tumor Cells Seeded into Previously Frozen Peripheral Blood Mononuclear Cells:
Antibody Composition of the Invention vs. CD45 Depletion Only Start Enriched Fraction
Cocktail % Purity % Purity Log Enrichment
Antibody Cocktail 0.001 21.4 4.3 Anti-CD45 only 0.001 6.2 3.8 Antibody Cocktail 0.03
42.8 3.2 Anti-CD45 only 0.03 6.6 2.4 Antibody Cocktail 0.02 35.7 3.3 Anti-CD45 only
0.02 5.4 2.4 Antibody Cocktail 0.01 40.4 3.5 Anti-CD45 only 0.01 11.8 3.0 Antibody
Cocktail 0.01 36.3 3.4 Antibody Cocktail 0.01 33.7 3.4 Anti-CD45 only 0.01 8.0 2.8
Antibody Cocktail 0.02 43.3 3.4 Anti-CD45 only 0.02 20.1 3.1 Antibody Cocktail 0.02
26.9 3.2 Antibody Cocktail 0.02 34.7 3.3 Anti-CD45 only 0.02 3.5 2.3

Detailed Description Paragraph Right (30):
A preferred antibody composition for removing differentiated hematopoietic cells and breast and lung carcinoma cells from a sample comprises the monoclonal antibodies 2B7.1 (glycophorin A), SK7 (CD3), MEM15 (CD14), 3G8 (CD16), ALB9 (CD24), 80H3 (CD66b), J4.119 (CD19), 6F10.3 (CD2), MY31 (CD56), or the monoclonal antibodies 10F7MN (glycophorin A), SK7 (CD3), 32D12 (CD24), MEM154 (CD16), MEM15 (CD14), 80H3 (CD66b) or B13.9 (CD66b), T199 (CD56), 6F10.3 (CD2), J4.119 (CD19), and one or more of the monoclonal antibodies specific for an antigen on the surface of a breast or lung carcinoma as set forth in Table 4. Most preferably the monoclonal antibodies specific for an antigen on the surface of cells from a breast carcinoma used in a composition of the invention are one or more of 5E11, H23A, 6E7, RAR, BerEp4 and BRST1.

Detailed Description Paragraph Right (42):
In one embodiment, the tumor cells are metastatic tumor cells derived from epithelial cancers of the bronchi, mammary ducts, reproductive system, gastrointestinal tract and urogenital tract such as lung carcinoma, breast carcinoma, colon carcinoma, prostate carcinoma and bladder carcinoma.

Detailed Description Paragraph Right (81):
One currently used method for enriching for non-hematopoietic tumor cells is to use a negative selection technique with antibodies specific for CD45. The inventors have compared their antibody composition with anti-CD45 alone on the ability to enrich peripheral blood mononuclear cells for breast carcinoma tumor cells and have shown that the antibody composition of the invention enriches the tumor cells 10 fold (1 log) over anti-CD45 alone.

Detailed Description Paragraph Right (97):
Tetramers of anti-breast carcinoma antibodies as shown in Table 4 were combined with a progenitor enrichment cocktail (D2.10, UCHT1, MEM15, 3G8, ALB9, 80H3, J4.119, 6F10.3, T199, and optionally 8D2.2, T16 and FA60152, or 10F7MN, UCHT1, 32D12, MEM154, MEM15 or B13.9, T199, 6F10.3, J4.119, and optionally, 8D2.2, T16 and 1VC7) to produce a cocktail for breast carcinoma purging and debulking. Including the lineage depletion increases the degree of tumor purge over that seen with just anti-tumor antibodies alone (Table 7). Breast carcinoma cell lines were added to previously frozen marrow, peripheral blood leukapheresis or fresh bone marrow. Tumor cell purges were performed using the anti-breast carcinoma antibodies indicated in Table 7 with and without the standard lineage depletion (progenitor enrichment cocktail). The recovery of hematopoietic progenitors during lineage depletion is given in Table 8. Enrichment of progenitors was generally 50 to 100 fold.

Detailed Description Paragraph Right (99):
Cells from the CAMA breast carcinoma cell line were mixed with previously frozen bone marrow (BM) and processed with the enrichment antibody composition (D2.10, UCHT1, MEM15, 3G8, 8OH3, J4119, 6F10.3, T199, 8D2.2, T16, FA6.152, and J33) in a one step magnetic depletion. The results shown in Table 9 demonstrates that the CAMA cells were enriched 2-3 log using the tumor enrichment antibody compositions.

Detailed Description Paragraph Right (100):
Cells from the CAMA breast carcinoma cell line were seeded into previously frozen peripheral blood mononuclear cells (PBMC) and processed with the enrichment antibodies capable of binding to glycophorin A (2B7.1), CD2 (6710.3), CD14 (MEM15), CD16 (3G8), CD38 (T16), CD45 (J33) and CD66b (80H3) in a one step magnetic depletion. The results shown in Table 10 demonstrate that CAMA cells were enriched up to 4.5 log.

Detailed Description Paragraph Right (101):
Cells from the CAMA breast carcinoma cell line were seeded into previously frozen peripheral blood mononuclear cells (PBMC) and processed with the enrichment antibodies capable of binding to glycophorin A (2B7.1), CD2(6710.3), CD14 (MEM15), CD16 (3G8), CD38 (T16), CD45 (J33) and CD66b (80H3). The results were compared with the common method of negative selection, ie. the use of anti-CD-45 alone. The results shown in Table 11, demonstrates that there is close to a ten fold (1 log) greater enrichment using the antibody composition of the invention, over negative selection with CD45.

Detailed Description Paragraph Center (14):
Purging Breast Carcinoma Cells (BT20 or T47D Cells)

Detailed Description Paragraph Center (16):
Enrichment of Breast Carcinoma Cells in Bone Marrow

CLAIMS:

9. A process according to claim 8 wherein the epithelial cancer is selected from the group consisting of lung carcinoma, <u>breast</u> carcinoma, colon carcinoma, prostate carcinoma and bladder carcinoma.